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(54) Title: TREATMENT WITH CALCIUM CHANNEL BLOCKERS FOR DRUG-INDUCED HYPERSENSITIVITY

(57) Abstract

Methods, compositions and devices for preventing and/or treating an adverse reaction of the skin to the presence of a skin-sensitizing agent by administering an effective amount of a calcium channel blocker alone or in combination with at least one diuretic and/or at least one glucocorticosteroid.

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TREATMENT WITH CALCIUM CHANNEL BLOCKERS FOR DRUG-INDUCED HYPERSENSITIVITY

1. Field of the Invention

The present invention relates to methods and compositions for preventing or treating adverse reactions of the skin in general to skin-sensitizing agents and especially adverse reactions occasioned by the cutaneous administration of a therapeutic agent for transdermal applications.

2. Background of the Invention

Allergic reactions of the skin to various agents, known as allergic contact dermatitis (ACD), is an immune response that occurs in the skin. The response is the result of the penetration of the skin by a foreign substance (e.g. hapten or antigen) that provokes a skin sensitization reaction. ACD is a two-phase process involving an initial induction phase followed by an elicitation phase.

The induction phase occurs immediately after first time exposure of the skin to the hapten or antigen and is characterized by the formation of immune memory cells that can subsequently recognize the specific hapten or antigen which previously entered the skin for the first time.

The elicitation phase occurs when the skin is subsequently re-exposed to the original hapten or antigen. In the elicitation phase, the skin provides an overt reaction to the presence of the hapten or antigen in the form of a skin inflammatory response.

ACD generally results in a life-time persistent memory for the specific hapten or antigen. Thus, when the skin is exposed to the hapten or antigen at a subsequent time, there is typically an immediate and often severe skin inflammatory response.

Agents that cause allergic contact dermatitis are varied and numerous and include, for example, metals (e.g. nickel, chromium, cobalt and the like) fragrances, chemicals, cosmetics, textiles, pesticides, plastics, pollen and the like (see, for example, R.J.G. Rycroft et al. "Textbook of Contact Dermatitis"). Therapeutic agents such as drugs may also cause allergic contact dermatitis particularly when administered transdermally.

The transdermal route of parenteral delivery of drugs provides many advantages over alternate routes of administration. Transdermal delivery systems (TDS) for delivery of drugs or other beneficial agents are well-known (see, for example, U.S. Patent Nos. 3,598,122, 3,598,123, 4,286,592, 4,314,557, 4,379,454, 4,599,222 and 4,573,995, which are each incorporated herein by reference). A TDS is generally composed of the following components: (a) "basic components", including backing, matrix

reservoir, and an optional separate adhesive layer; (b) the drug or other therapeutic agent; (c) "additives", including solubilizers, plasticizers and permeation enhancers; and (d) "impurities" such as residual amounts of monomers, initiators, cross-linkers, etc., from the polymerization process during fabrication of the basic components.

However, TDS provide conditions highly conducive for the induction of skin allergic reactions, and the following skin reactions may be expected to occur:

1. Irritant reactions to the drug, an additive, an impurity, or a combination thereof;
2. Allergic reactions, especially to the low molecular weight components (drug, additive, impurity, adhesive);
3. Prolonged skin occlusion causes blocking of sweat ducts favoring local sweat retention syndrome.

Allergic contact dermatitis presents a significant problem in the transdermal administration of therapeutic agents. It is well known that many drugs, including some currently marketed in the United States (e.g. clonidine) sensitize the skin when used in a transdermal delivery system. Skin inflammation may be produced not only by the transdermally delivered drug, but also

by a non-sensitizing drug combined with skin sensitizing permeation enhancers, or a combination of a sensitizing drug and a sensitizing permeation enhancer. Penetration of these sensitizing agents into the skin and the resulting skin irritation may persist well beyond the time that the transdermal patch is removed from the skin. The local inflammation may be a source of discomfort and a clinical complication in a patient suffering from such a reaction.

Efforts have been made to address the problem of allergic contact dermatitis by prophylactically treating the skin to prevent the onset of the induction phase of ACD and/or to therapeutically prevent or reduce the adverse effects of the elicitation phase of ACD. For example, U.S. Patent No. 5,202,130 discloses that lanthanide ions and organic calcium channel blockers individually can be used for the treatment of contact allergic dermatitis.

Wolfgang Diezel et al., J. Invest. Derm., Vol. 93, No. 3, pp. 322-326 (September 1989) discloses the sensitization of mice with 1-chloro-2, 4-dinitrobenzene and subsequent treatment with lanthanum citrate and diltiazem hydrochloride to prevent the onset of the induction phase of the sensitizing agent. Philip W. Ledger, et al., U.S. Patent No. 5,120,545 disclose the prevention of skin sensitization by the administration of an antigen processing-inhibiting agent such as ammonium chloride.

A method of preventing contact sensitization using steroids (e.g. corticosteroid and glucocorticoid carboxylic acid esters) is disclosed, for example, in Alfred Amkraut, U.S. Patent No. 5,118, 509 and Peter M. Ross, et al., U.S. Patent No. 4,897,260.

Methods of treating ACD through the blocking of the elicitation phase after initial exposure to a drug is disclosed, for example, in John McFadden, et al., J. Invest. Derm., Vol. 99, No. 6, pp. 784-786 (December 1992). Tuberculin-induced delayed-type hypersensitivity reaction in human skin was inhibited by topical application of verapamil hydrochloride prior to or concurrent with challenge with tuberculin.

Also, Richard L. Gallo, et al., Arch. Dermatol., Vol. 125, pp. 502-506 (April 1989) discloses the administration of the diuretic amiloride hydrochloride as a topical anti-inflammatory agent in the treatment of ACD, particularly mice sensitized with 2,4,6-trinitrobenzene.

As disclosed in U.S. Serial No. 08/198,003 filed February 17, 1994, and references cited therein, irradiation of skin with ultraviolet light B (UVB) is known to be immunosuppressive. These UVB effects are thought to be mediated, in part, by the UVB-induced isomerization of trans-urocanic acid (trans-UCA), a molecule which makes up about 0.5% of the total dry weight in the upper layers of human epidermis, to cis-urocanic acid (cis-UCA).

Cis-UCA is known to have various immunosuppressive actions in vivo in a number of experimental systems and is believed to act through histamine-like receptors in the skin. More recently, it has been shown that the UVB impairment of the induction phase of allergic contact dermatitis to epicutaneously applied haptens in certain mouse strains depended on the participation of the cytokine, tumor necrosis factor-a (TNFa). It has been suggested that local release of TNFa may inhibit sensitization by trapping epidermal Langerhans cells and preventing them from reaching the draining lymph node where they activate T. cells.

As further disclosed in U.S. Serial No. 08/198,003, mast cell degranulators such as cis-urocanic acid are effective for preventing or inhibiting the skin sensitizing or irritating effect of a transdermally administered therapeutic agent.

Despite these efforts and the knowledge gained regarding the cause of ACD, there remains a need to develop compositions which effectively prevent the onset of ACD or reduce the adverse affects of ACD after the person has been sensitized to an agent, as for example, a transdermally administered agent such as a drug.

In this regard, Applicants have gained the knowledge that there is a distinct process step implicated in the immune response associated with allergic contact dermatitis, which when

interfered with, results in the prevention and/or treatment of ACD. This process step referred to herein as cellular signal transduction, is believed responsible for the acquisition of memory by T-lymphocytes, for the cytokine-mediated regulation of antigen presentation and for other cellular processes as well.

Applicants have discovered that a particular class of compounds having anti-hypertensive properties, referred to herein as calcium channel blocking agents alone or in combination with at least one diuretic, or at least one glucocorticosteroid achieves significant improvement in the desensitization of a patient's skin. As a result, the reaction of the skin to a skin-sensitizing agent such as therapeutic agents administered transdermally is better controlled allowing for the administration of agents that could not previously be administered and/or have longer dosage regimens. The present invention therefore provides prevention and/or treatment of an adverse reaction to the skin, as well as a transdermal therapy which reduces discomfort to the patient.

SUMMARY OF THE INVENTION

The present invention is generally directed to methods and compositions of preventing or treating allergic contact dermatitis (ACD) and compounds and systems, especially transdermal systems, used in said methods. In one aspect of the

invention a method and composition is provided for preventing or treating an adverse reaction of the skin caused by the presence of skin-sensitizing agents such as metals, fragrances, cosmetics, textiles, pollen, pesticides, plastics and the like. The present invention is also applicable to ACD induced by the transdermal administration of an agent, as for example, a therapeutic agent such as a drug. The method of the present invention comprises administering to the skin of a warm-blooded animal an effective amount of at least one calcium channel blocking agent alone or in combination with at least one diuretic, and/or at least one glucocorticosteroid.

The agents employed in the present invention for preventing or treating skin irritation or inflammation from ACD caused by any skin-sensitizing agent can be prepared in the form of a composition containing one or more additives including skin permeation enhancers, excipients and the like.

These adverse skin reaction preventing or treating agents may be administered topically in the form of lotions, creams, sprays and the like, by non-cutaneous routes as well as through the use of transdermal patches. In transdermal applications, the agents may be administered from a single reservoir also containing a therapeutic agent or preferably from a separate reservoir of a transdermal patch.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is generally directed to methods and systems for preventing the onset of skin irritation or inflammation caused by allergic contact dermatitis by treatment before, after or during the induction phase of sensitization and for alleviating this condition once ACD has progressed to the elicitation phase. In one aspect of the invention the skin is treated with at least one calcium channel blocking agent alone or in combination with at least one diuretic, or at least one glucocorticosteroid.

Five calcium channel blocking compounds belonging to four classes of compounds with diverse chemical structures have been approved for clinical use in the United States. They are: the arylalkylamines (e.g., verapamil), the dihydropyridines (nicardipine, nifedipine, and nimoldipine), the benzothiazepines (diltiazem), and diphenylpiperazines (e.g., cinnarizine). In addition, a number of calcium channel blockers are also diuretics (e.g., perhexiline).

The pharmacological properties of calcium channel blockers have been well-examined (see Goodman and Gilman, Chapter 32, "Pharmacological Basis of Therapeutics", 8th Edition, McGraw-Hill, 1993). They inhibit the inward flux of extracellular calcium via voltage-sensitive or "potential-operated" channels

and thereby inhibit excitation and contraction coupling in cardiac and smooth muscle cells. In non-excitatory cells, they appear to inhibit cellular signal transduction by interfering with the generation of intracellular second messenger, calcium and cyclic nucleotides (e.g. cyclic AMP), that are indirectly coupled to "receptor-operated" calcium channels.

Examples of calcium channel blockers for use in the present invention include: nifedipine, verapamil, diltiazem, isradipine, bepridil, niludipine, becyclone, etafenone, perhexiline, nicardipine, flunarizine, nilvadipine, nisoldipine, nitrendipine, felodipine, cinnarazine, and nimoldipine.

Diuretics useful in the present invention include loop diuretics and potassium-sparing diuretics. The loop diuretics useful in the present invention are preferably selected from a group consisting of ethacrynic acid, furosemide and bumetanide. Potassium-sparing diuretics useful in the present invention include amiloride and triamterene.

The employment of a composition containing such adverse reaction skin preventing or treating agents provides desensitization of the skin to the presence of skin-sensitizing agents as encountered from a variety of sources including transdermal systems before, after or during the transdermal administration of the therapeutic agent.

Such adverse skin reaction preventing agents provide inhibition of the immune response and specific immune tolerance to the provoking antigen. More specifically, a single administration to the skin of at least one calcium channel blocker alone or in combination with at least one diuretic, or at least one glucocorticosteroid renders a warm-blooded animal specifically unresponsive to an antigen, a state known as immunological tolerance. Three immunosuppressive agents known to induce immune tolerance are UVB radiation, the cytokine TNF-α and cis-urocanic acid. A number of mechanisms are thought to be responsible for the induction and maintenance of this tolerant state. Regardless of the mechanism, it is well-known that tolerance to an antigen which stimulates a sensitization response can be induced first by presenting the antigen in a tolerogenic form or via a tolerogenic route. The present invention encompasses a method wherein the immune response of an antigen is suppressed and a state of prolonged immunological tolerance is achieved.

Calcium channel blockers employed in the present invention affect signal transduction. It is believed that these compounds function as calcium ion pump poisons in that they indirectly interfere with the homeostatically regulated ion balance in other cells. The balance of hydrogen, sodium and potassium ions is upset by changing the net flux of intracellular calcium ions. Consequently, all those cellular processes dependent on the

maintenance of homeostatically regulated intracellular ions are disrupted. In particular, the process of cellular signal transduction is known to be highly sensitive to changes in the level of intracellular ions, particularly calcium ions.

Glucocorticosteroids for use in the present invention include, for example, (a) hydrocortisone and analogs thereof, (b) beclomethasone, (c) betamethasone and analogs thereof, (d) clobetasol and analogs thereof, (e) desonide, (f) dexamethasone, (g) fluocinonide, (h) prednisone, and (i) triamcinolone. Hydrocortisone is the preferred gulcocorticosteroid.

The above methods are useful for preventing or treating skin sensitization or inflammation produced by a variety of skin-sensitizing agents such as, for example, a drug selected from, but not limited to, the following group: (a) an angiotensin converting enzyme inhibitor; (b) a beta adrenergic receptor blocker; (c) an anti-hypertensive drug other than an angiotensin converting enzyme inhibitor or a beta adrenergic receptor blocker; (d) an anti-histamine; (e) an anti-asthmatic; (f) a non-steroidal anti-inflammatory drug; (g) a central nervous system active drug; (h) a weight control drug; (i) an anticoagulant; (j) a potassium control drug; (k) an immunomodulatory drug; (l) a decongestant; and (m) proteins and peptides such as insulin and thyrotropin-releasing hormone.

More specifically, the therapeutic agents for administration in accordance with the present invention include all of the major therapeutic areas, including, but not limited to: anti-infectives, such as antibiotics and antivirals; analgesics and analgesic combinations; anorexics; antiarthritics; anti-asthmatics (such as albuterol, metaproterenol, ketotifen and terbutaline); anticoagulants (such as urokinase); anticonvulsants; antidepressants; anti-diabetics; antidiarrheals; antihistamines (such as chlorpheniramine and diphenhydramine); anti-inflammatory agents (such as ketoprofen, prostaglandins, flurbiprofen, diclofenac, indomethacin, piroxicam and ibuprofen); antimigrane agents; anti-motion sickness preparations; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics; antispasmodics, including gastrointestinal and urinary; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular agents, including angiotensin converting enzyme inhibitors (such as captropril and fosinopril); beta blockers (such as nadolol, timolol, propranolol and alprenolol); antiarrythmics; antihypertensives (such as clonidine); vasodilators, including general, coronary, peripheral and cerebral; central nervous acting agents (such as fluphenazine, trifluoperazine, haloperidol, Xanax®, Librium®, Valium®); cough and cold preparations; decongestants; diagnostics; hormones; hypnotics; muscle relaxants; parasympatholytics; parasympathomimetics;

psychostimulants; sedatives; weight control and appetite suppressive drugs (such as mazindol) and tranquilizers.

The present invention further provides an article useful for preventing or treating the skin sensitizing or inflammatory effect of a component of a transdermal drug delivery system, where the component is either a drug, a skin permeation enhancer or a combination of the two and the like, the article comprising:

(a) a transdermal delivery system comprising a therapeutic agent (e.g. a drug) of interest; and

(b) an effective amount of at least one calcium channel blocking agent alone or in combination with at least one loop diuretic, or at least one glucocorticosteroid.

The adverse skin reaction preventing or treating agents can also be administered in a transdermal or a controlled-release device. Examples of transdermal devices and delivery systems which may be used are disclosed in Bodde, H.E. et al., Crit. Rev. Ther. Drug Carrier Syst. 6:87-115 (1989); and in U.S. Patents No. 3,598,122, 3,598,123, 4,286,592, 4,314,557, 4,379,454, 4,559,222, 4,573,995, which references are hereby incorporated by reference.

The delivery system may include a first transdermal device comprising a matrix for placing the adverse skin reaction preventing or treating agents in transmitting relationship to the skin. A second transdermal device may be used to place the therapeutic agent in transmitting relationship to the skin after the adverse reaction preventing or treating agent has been transdermally administered to the skin. The first and second transdermal devices may be incorporated into a single transdermal patch.

The adverse skin reaction preventing or treating agents are administered by themselves or, in transdermal systems in combination with a therapeutic agent of interest. These agents may be administered topically or non-cutaneously such as by intradermally, intravenously, intramuscularly, orally or intraperitoneally. The agents of the present invention can be incorporated into a pharmaceutically acceptable composition for topical application to the skin in the form of lotions, creams gels and the like. Useful carriers for the preparations of such compositions include water, ethanol, gels and the like.

The precise formulation of the transdermally administered therapeutic agent (e.g. a drug) and the adverse skin reaction preventing or treating agents of the present invention can be designed to deliver the drug and the agents at the desired fluxes and can be in numerous forms, including, without limitation,

ointments, gels and creams. Aqueous formulations, in particular gels, typically comprise water and from about 1 to 2.5% (w/w) of a gelling agent such as hydroxyethylcellulose or hydroxypropylmethylcellulose (HPMC). Typical non-aqueous gels comprise silicone fluid or mineral oil. The mineral oil may also have from about 1 to 2% (w/w) of a gelling agent such as colloidal silicon dioxide. The suitability of a particular gel composition depends on the compatibility of its constituents with the drug (with or without a permeation enhancer) and the adverse skin reaction preventing or treating agents.

In another embodiment, the agents of the present invention are delivered to the skin prior to the administration of the therapeutic drug or drugs. Such prior administration can be via transdermal application using a device as described above, via topical application, intracutaneous injection, and the like.

In yet another embodiment, the agents are delivered by another non-cutaneous route and method of delivery, either concurrently with, or prior to, the transdermal administration of the therapeutic drug.

In all of the above embodiments, the dosage of the adverse skin reaction preventing or treating agents administered will be dependent upon the agent, the age, health, and weight of the

recipient, kind of concurrent treatment, if any, and frequency of treatment.

The methods and compositions within the scope of this invention include all compositions and methods wherein the adverse skin reaction preventing or treating agents are contained in an amount effective to achieve their intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art.

For transdermal administration, typical effective dosages of the agents to prevent and/or treat ACD by a sensitizing drug will depend on their permeation through human skin, and are a function of the physical properties of the permeant, including the partition coefficient of the permeant between solvent and skin, molecular weight and melting point. In general, the maximum flux that can be obtained from any permeant occurs from saturated solutions. Equations have been derived that predict accurately the maximum flux given the partition coefficient, molecular weight and melting point of the permeant as described in, for example, "TREATISE ON CONTROLLED DRUG DELIVERY", A. Kydonieus, ed., Marcel Dekker, Inc., New York, 1991, in particular, p. 370, equations 3a and 4a and p. 34, Figure 2, incorporated herein by reference. For example, for the transdermal delivery of the calcium channel blocker, e.g.

nifedipine, the expected maximum flux that can be delivered locally to skin is in the range of from about 0.1 to 20 $\mu g/cm^2/hr$. The expected maximum flux for the diuretic (e.g. ethacrynic acid) is from about 5 to 50 $\mu g/cm^2/hr$. For transdermal delivery of glucocorticosteroids, including the preferred agent hydrocortisone, the expected maximum flux that can be delivered locally to the skin is from about 0.005 to 5 $\mu g/cm^2/hr$.

These values are dependent, for example on varying skin age, skin type and skin condition. The preferred range for the maximum flux for the calcium channel blocker, e.g. nifedipine, is from about 0.5 to 5 $\mu g/cm^2/hr$. The preferred range for the diuretic is from about 10 to 25 $\mu g/cm^2/hr$. For administration of the glucocorticosteroid, the preferred maximum flux is from about 0.01 to 1.0 $\mu g/cm^2/hr$. Accordingly, as will be understood by those skilled in the art, the delivery of a particular agent, is controlled by the percent saturation of that agent in the chosen vehicle.

The amount of the calcium channel blocker, diuretic e.g. loop diuretic and/or potassium-sparing diuretic, or glucocorticosteroid which can be delivered to prevent or treat ACD will vary from patient to patient. For example, the amount of nifedipine delivered from a gel formulation (2.5% HPMC in 75% ethanol) is from about 0.1 to 5% by weight, and preferably from

about 0.25% to 2.0% by weight. The amount of diuretic e.g. loop diuretic such as ethacrynic acid, which is preferably used from the same gel formulation is in the range of from about 0.25% to 10% by weight. The amount of glucocorticosteroid which is preferably employed from the same gel formulation in the present invention is in the range of from about 0.1% to 5% by weight.

For administration of the adverse skin reaction preventing agents to prevent or treat skin sensitization, the dosage will vary as described. For example for topical application, the preferred agents are calcium channel blockers alone (e.g. nifedipine) or in combination with a diuretic (e.g. ethacrynic acid). In general, the amount of the calcium channel blockers (e.g. nifedipine) is from about 0.1 to 10% by weight, preferably from about 0.1 to 1.0% by weight based on the total weight of the composition.

The amount of the optional diuretic (e.g. ethacrynic acid) is typically from about 0.5 to 5% by weight, preferably from about 0.1 to 1.0% by weight based on the total weight of the composition.

The amount of the optional glucocorticosteroid is up to about 2.0% by weight, preferably from about 0.05 to 1.0% by weight.

Example 1

Nifedipine as a Counter Sensitizer to DNCB

A 0.5% (w/v) solution of nifedipine was prepared in a gel formulation (2.5% HPMC in 75% ethanol). The same gel formulation served as a negative control. For sensitization, a 1% (w/v) solution of dinitrochlorobenzene (DNCB) was prepared in acetone.

Twenty-four (24) Balb/c mice had their abdominal skin shaved. The mice were divided into three equal groups. The first group acted as a negative control and received on day 0 an application of 0.2 mL of hydroxypropylmethylcellulose (HPMC) on their exposed abdominal skin. The second group acted as a positive control by receiving on day 0, 0.2 mL of HPMC gel on exposed abdominal skin. The third group of mice was treated with 0.2 mL of HPMC gel containing nifedipine on day 0.

Twenty-four (24) hours later, the mice in Groups II and III received ten (10) microliters of 1% DNCB solution over the skin area pretreated with gel, while the mice in Group I received ten (10) microliters of acetone. All three groups were challenged on the right ear with twenty (20) microliters of 1% DNCB in acetone five (5) days after sensitization.

Adverse reaction to the challenge with DNCB was determined by measuring the thickness of the mice ears before and after

challenge to determine the amount of swelling, and then comparing the degree of swelling for mice treated in accordance with the invention (Group III) with Groups I and Groups II. The results are shown in Table 1.

TABLE I

TREATMENT	EAR THICKNESS (MM X 10^{-3})	EAR SWELLING (MM X 10^{-3})	% SUPPRESSION
GROUP I NONE (HPMC GEL) 24 HOURS	250 ± 10	-	-
GROUP II DNCB ONLY (100 µg) 24 HOURS	279 ± 17	29	-
GROUP III NIFEDIPINE 1 MG (IN HPMC GEL) (PRE ONLY) + DNCB (100 µg) 24 HOURS	254 ± 7	4	88

As shown in Table 1, the Group II mice exhibited significant ear swelling when sensitized to DNCB. The calcium channel blocker, nifedipine alone constituting an adverse skin reaction preventing agent when administered prophylactically limits inflammation induced by sensitization with DNCB.

Example 2

Nifedipine and Hydrocortisone as Counter Sensitizers to DNCB

The procedures of Example 1 were repeated except that the adverse skin reaction preventing or treating agent was a combination of a 1% (w/v) solution of hydrocortisone, and a 0.25% (w/v) solution of nifedipine, prepared in the above gel formulation. The results are shown in Table II.

TABLE II

TREATMENT	EAR THICKNESS ($MM \times 10^{-3}$)	EAR SWELLING ($MM \times 10^{-3}$)	% SUPPRESSION
NONE (HPMC GEL)			
24 HOURS	229 ± 9	-	-
48 HOURS	229 ± 7	-	-
DNCB ONLY (100 µg)			
24 HOURS	319 ± 23	91	-
48 HOURS	296 ± 11	68	-
(Hydrocortisone 2 mg + Nifedipine 0.5 mg) (in HPMC GEL) (PRE ONLY) + DNCB (100 µg)			
24 HOURS	272 ± 19	44	52
48 HOURS	277 ± 23	49	28

As shown in Table II, the Group II mice showed significant ear swelling when sensitized with DNCB. The combination of hydrocortisone and nifedipine constituting an adverse skin

reaction preventing or treating agent in accordance with the present invention suppressed adverse reactions induced by sensitization with DNCB.

Example 3

Ethacrynic acid and Nifedipine as Counter Sensitizers to DNCB

The procedures of Example 1 were repeated except that the adverse skin reaction preventing or treating agent was a combination of a 2.5% (w/v) solution of ethacrynic acid and a 0.25 % (w/v) of nifedipine solution prepared in the above HPMC gel. The results are shown in Table III.

TABLE III

TREATMENT	EAR THICKNESS ($MM \times 10^{-3}$)	EAR SWELLING ($MM \times 10^{-3}$)	% SUPPRESSION
GROUP I (HPMC GEL) 24 HOURS 48 HOURS	 239 ± 10 238 ± 10	 - -	 - -
GROUP II DNCB ONLY (100 µg) 24 HOURS 48 HOURS	 294 ± 12 314 ± 12	 55 76	 - -
GROUP III (NIFEDIPINE 0.5 MG + ETHACRYNIC ACID 0.5 MG IN HPMC GEL) (PRE ONLY) + DNCB (100 µg) 24 HOURS 48 HOURS	 263 ± 9 275 ± 17	 24 37	 56 51

As shown in Table III, the Group II mice exhibited significant ear swelling when sensitized with DNCB. The combination of nifedipine and ethacrynic acid constituting an adverse skin reaction preventing or treating agent in accordance with the present invention suppressed adverse reactions induced by sensitization with DNCB.

Example 4

Nifedipine as a Counter Sensitizer to Nadolol

Forty (40) CBA/J female mice were obtained from Jackson Labs. A 0.5% (w/v) solution of nifedipine was prepared in a gel formulation (2.5% HPMC in 75% ethanol). A 5% (w/v) solution and a 1% (w/v) solution of nadolol were also prepared. In addition a 2.5% HPMC solution was prepared as a placebo.

The mice were shaved on their back. Positive control mice (10) received the placebo and the 5% nadolol solution on alternating days for three weeks. The experimental mice (10) received the nifedipine solution and the 5% nadolol solution on alternating days for three weeks.

A negative control group of mice (20) received the placebo gel on each day for three weeks.

Five days after the last application each group of mice were challenged on the right ear with the 1% nadolol solution and on the left ear with the placebo gel. The thickness of the ears was measured after 24, 48, and 72 hours. The results are shown in Table IV.

TABLE IV

TREATMENT	EAR SWELLING (MM X 10^{-3})	% SUPPRESSION
GROUP I		
NONE (HPMC GEL)		
24 HOURS	-	-
48 HOURS	-	-
72 HOURS	-	-
GROUP II		
NADOLOL ONLY		
24 HOURS	28	-
48 HOURS	50	-
72 HOURS	50	-
GROUP III		
NIFEDIPINE + NADOLOL		
24 HOURS	0	100
48 HOURS	10	80
72 HOURS	0	100

As shown in Table IV, the Group II mice exhibited significant ear swelling when sensitized to nadolol. Nifedipine alone constituting an adverse skin reaction preventing or treating agent limited adverse reactions induced by sensitization with nadolol.

Example 5

Verapamil as a Counter Sensitizer to Nadolol

The procedures of Example 4 were repeated except that a 0.5% (w/v) solution of verapamil was used in place of nifedipine. The results are shown in Table V.

TABLE V

TREATMENT	EAR SWELLING ($MM \times 10^{-3}$)	% SUPPRESSION
GROUP I		
NONE (HPMC GEL)		
24 HOURS	-	-
48 HOURS	-	-
72 HOURS	-	-
GROUP II		
NADOLOL ONLY		
24 HOURS	28	-
48 HOURS	50	-
72 HOURS	50	-
GROUP III		
VERAPAMIL + NADOLOL		
24 HOURS	30	0
48 HOURS	29	42
72 HOURS	20	60

As shown in Table V, the Group II mice exhibited significant ear swelling when sensitized to nadolol. Verapamil alone constituting an adverse skin reaction preventing or treating agent limited adverse reactions induced by sensitization with nadolol.

WHAT IS CLAIMED IS:

1. A method of preventing or treating an adverse reaction of the skin of a warm-blooded animal to the presence of a skin-sensitizing agent comprising administering to said warm-blooded animal an effective amount of an adverse skin reaction preventing or treating agent comprising at least one calcium channel blocker alone or in combination with at least one of a diuretic or glucocorticosteroid to said warm-blooded animal.

2. The method of claim 1 wherein the skin-sensitizing agent is a drug.

3. The method of claim 1 wherein the skin-sensitizing agent is administered transdermally.

4. The method of claim 1 where said adverse skin reaction preventing or treating agent is administered transdermally.

5. The method of claim 3 where said adverse skin reaction preventing or treating agent is administered transdermally.

6. The method of claim 5 comprising administering said adverse skin reaction preventing or treating agent and the skin-sensitizing agent from a transdermal patch.

7. The method of claim 1 wherein the calcium channel blockers are selected from the group consisting of arylalkylamines, dihydropyridines, benzothiazepines and diphenylpiperazines.

8. The method of claim 1 wherein the calcium channel blockers are selected from the group consisting of nifedipine, verapamil, diltiazem, isradipine, bepridil, niludipine, becyclone, etafenone, perhexiline, nicardipine, flunarizine, nilvadipine, nisoldipine, nitrendipine, felodipine, cinnarazine, and nimoldipine.

9. The method of claim 1 wherein the diuretic is selected from the group consisting of loop diuretics and potassium-sparing diuretics.

10. The method of claim 9 wherein the loop diuretic is selected from the group consisting of ethacrynic acid, furosemide and bumetanide.

11. The method of claim 10 wherein the loop diuretic is ethacrynic acid.

12. The method of claim 9 wherein the potassium-sparing diuretic is selected from the group consisting of amiloride and triamterene.

13. The method of claim 1 wherein the glucocorticosteroid is selected from the group consisting of hydrocortisone and analogs thereof, beclomethasone, betamethasone and analogs thereof, clobetasol and analogs thereof, desonide, dexamethasone, fluocinonide, prednisone, and triamcinolone.

14. The method of claim 13 wherein the glucocorticosteroid is hydrocortisone.

15. The method of claim 4 wherein the maximum flux of the calcium channel blocker is from about 0.1 to 20 $\mu g/cm^2/hr$.

16. The method of claim 15 wherein the maximum flux of the calcium channel blocker is from about 0.5 to 5 $\mu g/cm^2/hr$.

17. The method of claim 4 wherein the maximum flux of the diuretic is from about 5 to 50 $\mu g/cm^2/hr$.

18. The method of claim 17 wherein the maximum flux of the diuretic is from about 10 to 25 $\mu g/cm^2/hr$.

19. The method of claim 4 wherein the maximum flux of the glucocorticosteroid is from about 0.005 to 5 $\mu g/cm^2/hr$.

20. The method of claim 19 wherein the maximum flux of the glucocorticosteroid is from about 0.1 to 1.0 $\mu g/cm^2/hr$.

21. The method of claim 1 comprising administering to the warm-blooded animal an amount of said adverse skin reaction preventing or treating agent sufficient to treat or prevent allergic contact dermatitis caused by a skin-sensitizing agent in the form of a gel, said amount of the calcium channel blocker being from about 0.1 to 10% by weight, the amount of the diuretic being from about 0.05 to 5% by weight, and the amount of the glucocorticosteroid being up to about 2% by weight.

22. The method of claim 21 wherein the amount of the calcium channel blocker is from about 0.1 to 1.0% by weight, the amount of the diuretic is from about .1 to 1.0% by weight and the amount of the glucocorticosteroid being from about 0.05 to 1% by weight.

23. A composition for preventing or treating an adverse reaction of the skin of a warm-blooded animal to the presence of a skin-sensitizing agent comprising an effective amount of an adverse skin reaction preventing or treating agent comprising at least one calcium channel blocker alone or in combination with at least one of a diuretic or glucocorticosteroid.

24. A transdermal delivery system for transdermally administering an effective amount of an adverse skin reaction preventing or treating agent comprising a calcium channel blocker alone or in combination with at least one diuretic or at least one glucocorticosteroid, said system comprising:

(a) a first transdermal device comprising a matrix for placing the adverse skin reaction preventing or treating agent in transmitting relationship to the skin; and

(b) a second transdermal device comprising a matrix for placing a therapeutic agent in transmitting relationship to the skin after the adverse skin reaction preventing or treating agent has been transdermally administered to the skin from the first transdermal device.

25. The transdermal delivery system of claim 24 wherein the first and second transdermal devices are contained within a single transdermal patch.

26. A method of transdermally administering to a warm-blooded animal a therapeutic agent without thereby eliciting an adverse reaction from the skin comprising transdermally administering before, after or during the administration of the therapeutic agent an effective amount of an adverse skin reaction preventing agent comprising a calcium channel blocker alone or in combination with at least one diuretic or at least one glucocorticosteroid to said warm-blooded animal.

27. The method of claim 26 wherein the calcium channel blockers are selected from the group consisting of arylalkylamines, dihydropyridines, benzothiazepines and diphenylpiperazines.

28. The method of claim 26 wherein the calcium channel blockers are selected from the group consisting of nifedipine, verapamil, diltiazem, isradipine, bepridil, niludipine, becyclone, etafenone, perhexiline, nicardipine, flunarizine, nilvadipine, nisoldipine, nitrendipine, felodipine, cinnarazine, and nimoldipine.

29. The method of claim 26 wherein the diuretic is selected from the group consisting of loop diuretics and potassium-sparing diuretics.

30. The method of claim 29 wherein the loop diuretic is selected from the group consisting of ethacrynic acid, furosemide and bumetanide.

31. The method of claim 30 wherein the loop diuretic is ethacrynic acid.

32. The method of claim 29 wherein the potassium-sparing diuretic is selected from the group consisting of amiloride and triamterene.

33. The method of claim 26 wherein the glucocorticosteroid is selected from the group consisting of hydrocortisone and analogs thereof, beclomethasone, betamethasone and analogs thereof, clobetasol and analogs thereof, desonide, dexamethasone, fluocinonide, prednisone, and triamcinolone.

34. The method of claim 33 wherein the glucocorticosteroid is hydrocortisone.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/18760

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61F 13/00
US CL :424/449

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/447, 448, 449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 5,202,130 A (GRANT ET AL.) 13 April 1993, column 1, lines 26-57; column 4, line 38 through column 5, line 55.	1-5,7,8,23, 26-28 --- 1-34
Y	Chem. abstr., Vol. 121, No. 11, 12 September 1994 (Columbus, OH, USA), page 57, column 2, the abstract No. 124876b. REDRUP, A.C. et al. 'Effect of loop diuretics on rat peritoneal and human lung mast cells.' Agents Actions. 1994, 41 (Spec. Conf. Issue), C47-C48 (Eng).	1-34

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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08 JANUARY 1997

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/18760

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GALLO et al. Inhibition of allergic contact dermatitis and ultraviolet radiation-induced tissue swelling in the mouse by topical amiloride. Arch. Dermatol. April 1989, Vol. 125, page 502-506.	1-34
Y	US 5,077,054 A (AMKRAUT ET AL.) 31 December 1991, column 2, lines 31-41; column 4, lines 46-61; column 2, lines 49-55; column 4, line 63 - column 5, line 25.	1-34
Y	US 4,897,260 A (ROSS ET AL.) 30 January 1990, column 3, lines 24-46; column 8, line 16; column 12, line 57; column 7, lines 1-68 and column 1, lines 66-67.	1-34